Late Enlargement of Radiofrequency Lesions in Infant Lambs
Implications for Ablation Procedures in Small Children

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Background Despite the current clinical use of radiofrequency (RF) catheter ablation in infants, the acute and late effects of RF lesion production in immature myocardium remain unknown. This study was specifically designed to investigate the pathology of RF lesions in developing sheep myocardium.

Methods and Results In study 1, RF lesions were made on the epicardial left ventricular surface of the beating heart in 15 sheep, 5 approximately 4 weeks of age (11.0±1.0 kg) and 10 approximately 8 weeks of age (23.8±3.4 kg), to assess the effects of RF application duration (10 to 90 seconds) and electrode tip temperature (45°C to 90°C) on lesion size in immature myocardium. Lesion width and depth increased asymptotically with RF duration, to 7.0±0.7 and 4.8±1.0 mm at 90 seconds, respectively. The time to reach one-half lesion size was 6.5 seconds for width and 12.0 seconds for depth. Lesion width increased nearly linearly with tip temperature above 50°C, but depth followed a sigmoid relation, with no increase above 80°C. In study 2, RF lesions were made in all four cardiac chambers under fluoroscopic guidance in 19 infant sheep (10.9±1.4 kg). Lesion sizes and histological characteristics were assessed acutely (acute, n=5), at 1.07±0.02 months (1 month, n=5), and at 8.5±0.5 months (late, n=9). Atrial and ventricular lesions but not atrioventricular groove lesions apparently increased in size during the follow-up period. Atrial lesions width increased from 5.3±0.5 to 8.7±0.7 mm at 1 month (164%) but did not increase further at late follow-up, while ventricular lesion width increased from 5.9±0.8 to 10.1±0.7 mm (171%) at late follow-up but was not significantly changed at 1 month. Histological evaluation revealed replacement of normal myocytes with fibrous and elastic tissue at 1 month and late follow-up in all locations but also demonstrated a poorly delineated border with multiple extensions of fibrous and elastic tissue into surrounding normal myocardium in late ventricular lesions.

Conclusions RF lesion formation in immature sheep myocardium is similar to that in adult myocardium acutely but is associated with late lesion enlargement and fibrous tissue invasion of normal myocardium. These findings may have implications for clinical RF ablation procedures in infants.

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Key Words • catheter ablation • radiofrequency • infants

A ccessory atrioventricular (AV) pathway ablation with catheter-delivered radiofrequency (RF) energy has now become the treatment of choice for adults and most pediatric patients with accessory pathway–mediated arrhythmias that are either life threatening or refractory to medical therapy.1-4 In addition, RF ablation has been used to successfully eliminate or modify either slow or fast pathway conduction tissue in AV nodal reentry tachycardia,5 foci responsible for ectopic atrial tachycardia,6 and the tissue critical to some forms of ventricular tachycardia.7,8 Although the short- and medium-term safety of producing RF lesions around the AV groove and in the ventricle has now been established in both adult animals9 and humans,1-4 there have been no studies examining these lesions in developing myocardium.

This study examines the pathology of RF energy on lesions in immature developing myocardium by assessing lesion characteristics, first as a function of RF pulse duration and catheter tip temperature,10 then as a function of body growth.

Methods

Two sets of experiments were performed. The first experiments (study 1) were performed through a thoracotomy on the epicardial surface in 15 infant sheep to assess the effects of RF lesion duration and electrode tip temperature on young myocardium in a well-controlled setting. The second experiments (study 2) were performed using intravascular catheters to produce RF lesions on the endocardial surface in 19 infant sheep, which were then allowed to age between 1 and 9 months after lesion production to assess the effects of animal growth on RF lesion characteristics. All experiments were performed under protocols approved by the Animal Resources Committee at Children's Hospital, Boston.

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Study 1

Under general anesthesia with halothane and intravenous ketamine (10 mg/kg per hour), a left thoracotomy was performed on each of the 15 sheep. The left ventricular epicardial surface of the beating heart was exposed by creation of a pericardial cradle. The exposed heart was bathed in saline at 37°C to 38°C. RF energy was applied to multiple sites on the epicardial surface of each heart through a 6F electrode catheter with a 2-mm-long lumen tip (Bard) modified with a tip-mounted thermistor probe. A 500-kHz RF generator (Radionics) was used for RF energy delivery and for continuous monitoring of thermistor temperature. The catheter tip was maintained perpendicular to the epicardial surface, and cathe-
ter tip–tissue contact pressure was maintained constant with a 20-g weight. Electrode catheter tip temperature, a measure of tissue temperature at the electrode site, was monitored continuously during lesion production.

In 5 approximately 8-week-old sheep (24.9±4.2 kg), separate epicardial lesions were produced at electrode catheter tip temperatures ranging from 45° to 90°C in 5° increments. Duration of lesion production was 90 seconds for each lesion. In 10 sheep (5 approximately 4 weeks old, 11.0±1.0 kg, and 5 approximately 8 weeks old, 22.8±1.0 kg) separate epicardial lesions were produced at a constant electrode tip temperature of 80°C at durations varying from 10 to 90 seconds in 10-second intervals. After a minimum of 30 minutes after the last lesion was produced, the animals were euthanized for examination of the heart. Lesion size was determined after the bisected edge of each lesion was stained in a buffered solution of nitroblue tetrazolium. The lesions were measured on the epicardial surface to obtain width and on the cut surface to obtain depth.

The data were assessed for changes in lesion dimensions as a function of both lesion duration and tip temperature. The data for lesion size as a function of time were treated as an inverse exponential function of the form

\[ A = A_0 \times e^{-t/T} \]

where \( A \) is the dimension, \( A_0 \) is the dimensional asymptote, and \( T \) is the time constant for the rise in dimension. The duration that produced half the asymptotic dimension was defined as \( T_{1/2} \). Lesion characteristics at each RF duration were compared between the larger and smaller animals using ANOVA for repeated measures.

Study 2

Nineteen infant sheep between 8.2 and 12.8 kg (10.9±1.4) were studied. Each animal was sedated with an intramuscular injection of ketamine 5 mg/kg. An intravenous line was then placed and used to administer additional doses of ketamine to maintain light anesthesia. A 7F sheath (US Catheter and Instruments) then was inserted into one femoral artery and one femoral vein. A 7F quadrupolar, deflectable-tipped catheter with a 4-mm tip then was placed through either the venous or arterial sheath to access the right atrium and ventricle (venous sheath) and the left atrium and ventricle (arterial sheath). Intracardiac electrograms from the distal and proximal pairs of electrodes of the quadrupolar catheter were filtered from 30 to 250 Hz and continuously monitored on an Electronics for Medicine VR12 recorder, simultaneous with a standard lead II surface ECG. Using a combination of fluoroscopic and ECG guidance, the catheter tip was positioned at multiple points within each atria, ventricle, and along the AV groove. AV groove positions were located on both the atrial and ventricular sides of the tricuspid and mitral rings.

Ablation Protocol

Once positioned and electrically and fluoroscopically stable, the distal pole of the quadrupolar catheter was connected to the active lead of a 500-kHz RF generator (RFG-3C, Radionics, Inc.). The anatomic location of the catheter within the heart was noted, and RF energy was delivered in a unipolar fashion between the active lead and a large skin reference electrode positioned on the animal's lower back. During each application, power, voltage, current, and impedance were continuously monitored. Power was set at 20 W for the first 5 sheep, but because of frequent impedance rises and arrhythmias when making ventricular lesions was reduced to 15 W in the remaining 14 sheep. Lesion duration was set at 60 seconds, but in the occurrence of a sudden rise in impedance, the application was terminated and the catheter tip examined for coagulum formation and cleaned.

Postablation Protocol

After the final RF applications were made, the catheters were removed and examined, and the sheep were either euthanized after approximately 30 minutes of observation (n=5, acute) or recovered for 24 hours and sent to a long-term animal care facility for growth (n=14). Five of the 14 sheep were returned after 1.07±0.02 months (1-month group), and the remaining 9 were returned after 8.5±0.5 months (late group). Coronary angiography was performed in the late group before euthanasia and analysis. No sheep died during the follow-up phase.

After euthanasia, all hearts were treated similarly. The hearts were rapidly excised, washed, and the epicardial surface carefully examined for any lesions, with particular observation of areas where the original RF applications were predicted to be. Lesions on the epicardial surface were measured, and characteristics such as color, consistency, contour, and the presence of hemorrhage were noted. The hearts then were opened, carefully avoiding visually apparent RF lesions, and the endocardial surface of all four chambers were examined for any evidence of lesions. The locations and total number of lesions present were compared with the locations and number of RF applications made during the catheter procedure, and notations of "missing" lesions were made during the examination. Each lesion then was individually excised, and the endocardial dimensions were recorded. For lesions with an eccentric endocardial profile, lesion width or diameter was estimated as the average of the longest and shortest endocardial dimensions. Finally, the lesions were transected through their largest endocardial extent and their transmural depth noted, as well as any evidence that the lesion was transmural. Histological sections were prepared from the cut myocardial surface of the lesions using the following stains: hematoxylin and eosin for evaluation of tissue viability, Gomori's trichrome for evaluation of connective tissue, and the Verhoeff-van Gieson stain for evaluation of elastic tissue.

Statistical Analysis

ANOVA was used to compare data between the three experimental groups: acute, 1-month, and late. A post hoc comparison using the Bonferroni \( t \) test then was performed to identify specific differences between the acute group and the 1-month group and between the 1-month group and the late group. Differences in numbers of lesions found at various anatomic locations were evaluated with \( \chi^2 \) statistics. A value of \( P<.05 \) was considered significant. Data are mean±SD except where indicated.

Results

Study 1

Lesion width and depth increased as a function of both temperature and duration, but with distinctly different patterns and with some differences noted between lesion width and depth. Applied power varied from 0.7±0.2 W for 45°C lesions to 4.3±0.6 W for 90°C lesions. For the 80°C, variable-duration lesions, the initial applied power was 3.8±0.6 W, but the power required to \( k \times \rho \) the temperature at 80°C increased gradually during the application.

Effects of Age and Size

There was no difference in lesion widths or depths as a function of duration between the smaller 4-week-old sheep and the larger 8-week-old sheep. Therefore, the data for duration were combined into a single evaluation for all 10 sheep of both sizes.

Effects of Duration

At each duration, there was a wide variance in the lesion dimensions among the sheep, with lesion widths
and depths at 10 seconds ranging from 0.1 to 7.0 mm and 0.5 to 3.0 mm, respectively. At longer durations, the average variance was somewhat less, but lesion widths still ranged from 4.0 to 9.0 mm and depths from 2.5 to 8.5 mm at a single duration greater than 30 seconds. The average width increased from 4.2±2.5 mm at 10 seconds to 7.0±0.7 mm at 90 seconds, while the average depth increased from 1.7±1.1 mm at 10 seconds to 4.8±1.0 mm at 90 seconds, both increasing exponentially to an asymptote with time (Fig 1). The asymptote A_w was 6.3 mm for width and 4.2 mm for depth, yielding T_w values of 6.5 seconds for width and 12 seconds for depth. Of note, the asymptotic width was less than twice the asymptotic depth.

**Effects of Temperature**

There was only a minimally detectable lesion for tip temperatures below 50°C. Above 50°C, the width increased approximately linearly with temperature; however, the depth had more of a sigmoid relation to tip temperature, not increasing linearly until 65°C and not increasing any further above 80°C (Fig 1).

**Study 2**

Sheep size significantly increased between the initial catheter ablation procedure and both the 1-month and late follow-ups (P<.001, Table 1). Of 222 RF applications, 36 (16%) were terminated before 60 seconds because of an impedance rise, yielding an average energy delivery of 946 J (Table 2). Of the 222 RF applications, 144 (65%) were identified at postmortem examination, with the highest percentage of lesions found in the ventricle (79%) compared with 66% in the atrium (not significant by χ^2 analysis; see Table 2) and 52% on the AV groove (P<.001 by χ^2; Table 2).

Coronary angiography performed before euthanasia revealed normal left and right coronary circulations in all 9 late animals.

**Gross Findings**

The gross appearance of the acute lesions was similar in all three locations. The endocardial and myocardial surfaces generally revealed pale round or oval areas well demarcated from the surrounding tissue by a thin hyperemic rim. Some lesions, generally those associated with an impedance rise, had a small ulcerated area that sometimes had bits of coagulum adherent to the edges. A few lesions also had small areas of intramyocardial hemorrhage. Transmural lesions were noted in all chambers at all stages but were by far most frequent in the atria, where 90% of lesions were transmural versus 13% on the AV groove and 21% in the ventricle (P<.001 by χ^2 for both comparisons, Table 2). When an epicardial extension of an endocardial lesion could be identified, it usually had a similar appearance to the endocardial surface except that it was smaller and never associated with ulceration, adherent coagulum, or hemorrhage. Most lesions could be detected by palpation as a somewhat thickened and denser area of tissue.

The 1-month and late lesions grossly appeared quite similar to each other, with the exception that some of the late lesions were extremely large (Fig 2). Lesions were pale to pearly white, with smooth but sometimes irregular borders and a dense feeling consistent with fibrosis. As shown in Fig 2 and detailed in Table 2, most atrial (90%) and some ventricular (21%) lesions were transmural and associated with thinning of the myocardium, which resulted in an area of either dimpling or aneurysm of the epicardial surface. Atrial lesions were thinner than ventricular ones (Table 2). When assessing the depth of AV groove lesions, the exact division between the lesion and the myocardial surface was more difficult to identify than in other locations because of the fibrous nature of the normal AV ring.

**Lesion Size**

Fig 3 and Table 2 detail the lesion size data as a function of lesion location and observation time. For atrial lesions, the width but not the depth was significantly larger at the 1-month follow-up than at the acute evaluation but remained unchanged at the late follow-up compared with 1-month follow-up. Although the maximum size of AV groove lesions was larger at the 1-month and late assessments than at the acute assessment, the average size of AV groove lesions was similar at all three observation points. As with the atrial lesions,

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**Table 1. Sheep Growth During Follow-up: Study 2**

<table>
<thead>
<tr>
<th></th>
<th>Animals, n</th>
<th>Initial Weight, kg</th>
<th>Final Weight, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>5</td>
<td>10.7±1.1</td>
<td>...</td>
</tr>
<tr>
<td>1 Month</td>
<td>5</td>
<td>11.4±1.8</td>
<td>17.3±0.9</td>
</tr>
<tr>
<td>Late</td>
<td>9</td>
<td>10.7±1.2</td>
<td>45.2±5.6</td>
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</tbody>
</table>

*Significantly different from initial weight, P<.001.
TABLE 2. Radiofrequency Application and Lesion Characteristics by Cardiac Chamber and Evaluation Stage for Sheep in Study 2

<table>
<thead>
<tr>
<th>Lesion Characteristics</th>
<th>Power, W</th>
<th>Impedance, Ω</th>
<th>Duration, seconds</th>
<th>Impedance Rise, n (%)</th>
<th>Lesions Found, n (%</th>
<th>Transmural, n (% lesions found</th>
<th>Width, mm</th>
<th>Depth, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrium</strong></td>
<td></td>
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<tr>
<td>Acute</td>
<td>14</td>
<td>18.9±2.1</td>
<td>131±17</td>
<td>58±8</td>
<td>1 (7)</td>
<td>8 (57)</td>
<td>7 (88)</td>
<td>5.3±1.4</td>
</tr>
<tr>
<td>1 Month</td>
<td>17</td>
<td>17.3±2.0</td>
<td>135±21</td>
<td>56±9</td>
<td>5 (29)</td>
<td>11 (65)</td>
<td>10 (90)</td>
<td>8.7±4.3</td>
</tr>
<tr>
<td>Late</td>
<td>31</td>
<td>15.4±1.4</td>
<td>141±17</td>
<td>54±15</td>
<td>5 (16)</td>
<td>22 (71)</td>
<td>20 (90)</td>
<td>8.8±3.3</td>
</tr>
<tr>
<td>All stages</td>
<td>62</td>
<td>11 (18)</td>
<td>41 (66)</td>
<td>37 (90)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>AV groove</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Acute</td>
<td>29</td>
<td>18.3±2.7</td>
<td>129±17</td>
<td>60±0</td>
<td>1 (4)</td>
<td>13 (45)</td>
<td>1 (6)</td>
<td>6.3±2.0</td>
</tr>
<tr>
<td>1 Month</td>
<td>24</td>
<td>17.0±2.2</td>
<td>133±23</td>
<td>58±9</td>
<td>2 (8)</td>
<td>19 (79)</td>
<td>2 (10)</td>
<td>5.4±2.6</td>
</tr>
<tr>
<td>Late</td>
<td>35</td>
<td>15.1±0.5</td>
<td>134±21</td>
<td>56±11</td>
<td>5 (14)</td>
<td>14 (40)</td>
<td>3 (21)</td>
<td>6.9±3.3</td>
</tr>
<tr>
<td>All stages</td>
<td>88</td>
<td>8 (9)</td>
<td>46 (52)</td>
<td>6 (13)</td>
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<tr>
<td><strong>Ventricle</strong></td>
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<tr>
<td>Acute</td>
<td>17</td>
<td>17.9±2.6</td>
<td>139±14</td>
<td>56±9</td>
<td>3 (2)</td>
<td>15 (88)</td>
<td>2 (13)</td>
<td>5.9±2.5</td>
</tr>
<tr>
<td>1 Month</td>
<td>23</td>
<td>17.3±2.3</td>
<td>133±30</td>
<td>56±13</td>
<td>5 (22)</td>
<td>18 (78)</td>
<td>4 (22)</td>
<td>7.4±2.5</td>
</tr>
<tr>
<td>Late</td>
<td>32</td>
<td>15.1±0.4</td>
<td>136±18</td>
<td>54±16</td>
<td>9 (28)</td>
<td>24 (75)</td>
<td>6 (25)</td>
<td>10.1±3.3</td>
</tr>
<tr>
<td>All stages</td>
<td>72</td>
<td>17 (24)</td>
<td>57 (79)</td>
<td>12 (21)</td>
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<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>222</td>
<td>36 (16)</td>
<td>144 (65)</td>
<td>55</td>
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</tbody>
</table>

the ventricular lesion widths were larger at 1 month than at the acute measurements; however, in contrast to the atrial data, both the width and depth were larger at the late assessment than at the 1-month assessment. There were no significant differences between the size of transmural and nontransmural lesions in any location for acute, 1-month, or late lesions; however, all but a few atrial lesions were transmural, whereas most AV groove and ventricular lesions were not, potentially biasing size comparisons within each group.

Histological Findings

Histological examination of the acute lesions from all chambers with hematoxylin and eosin stain revealed coagulation necrosis with marked destruction of the myofibril architecture and prominent contraction band necrosis. As noted with vital staining of the gross specimens, most atrial lesions and a few ventricular and AV groove lesions were transmural. Collagen and elastic tissue content was similar to the normal surrounding myocardium.

Late and 1-month atrial lesions were similar histologically. They were well delineated with replacement of normal myocardial cells by fibrous and elastic tissue. Ventricular lesions at 1 month also demonstrated replacement of normal cells by fibrous and elastic tissue, but in contrast to the 1-month lesions, late lesions were often poorly delineated from the surrounding myocardium, with multiple extensions of fibrous and elastic tissue (Fig 4). Late and 1-month AV groove lesions revealed marked thinning of the normal myocardial tissue layer with replacement of muscle cells by fibrous and elastic tissue similar to that seen in the atrial lesions. Most areas were covered by a normal distribution of fat and fibrous tissue. Extensions of the late AV groove lesions into the ventricle were often associated with poor delineation of normal and abnormal myocardium, similar to that seen with late ventricular lesions.

Discussion

The primary findings of this study are first that immature myocardium in infant sheep appears to respond acutely to heating with RF energy in a manner similar to that observed in adult animals. With one exception (see below), the biophysical responses of the tissue as well as the gross and histological findings for the acute lesions in this study were nearly identical to those described previously from studies performed on
adult dog and human hearts.\textsuperscript{9-13} Second, and perhaps more important, in contrast to RF lesions made in adult myocardium,\textsuperscript{9,11-13} lesions in immature atrial and ventricular myocardium appear to increase in size during early rapid organ growth. Finally, at late follow-up, RF lesions in immature myocardium appear histologically more invasive than lesions in adult hearts,\textsuperscript{9,11,12} with extensions of fibrous and connective tissue that appear to cross the acute area of cell death into previously normal myocardium. These findings, which presumably result from differences in either the inflammatory response or the potential for cell growth in developing myocardium,\textsuperscript{14,15} may have implications for the performance of RF ablation in infant hearts.

**Acute Response**

In agreement with previous studies in adult animal hearts,\textsuperscript{10,16} the epicardial data from study 1 demonstrated that RF lesion size in immature myocardium is dependent on both application duration and catheter tip temperature. In fact, the specific characteristics of the relations between lesion size and application duration were in most ways nearly identical to those described previously.

Lesion size as a function of duration was well described by an inverse exponential rise with time and a time to one-half size of 6.5 seconds for width and 12 seconds for depth. These values are very close to that of 9 seconds, found by Wittkampf et al\textsuperscript{17} for the half time of the change in the average dimension of lesions made in dog hearts with a catheter in vivo. Of note, the half time was shorter for lesion width than for lesion depth, but the average depth was more than one-half the width. The first of these observations may be due to the in vivo myocardial perfusion and the absence of superfusion present in this study, factors that might promote deep tissue cooling and enhance superficial heating. No previous studies have applied RF energy in vivo under direct observation in controlled conditions. The latter observation that the depth was more than one-half the width may be related to the structure of the catheter tip,\textsuperscript{18,19} 2-mm length and radius, which when fully immersed in tissue provides a radial profile, which is 2 mm into the tissue but only 1 mm along the plane parallel to the epicardial surface. In addition, the catheter tended to slowly sink into the tissue during lesion production, also enhancing the lesion depth.

![Gross appearance of late ventricular and atrial lesions.](image)

**Fig 2.** Gross appearance of late ventricular and atrial lesions. Late lesions were occasionally very large and obvious at gross examination. Note thinned, dimpled areas in right ventricular free wall (white arrow) and in left atrial free wall (black arrow).
It should also be noted that the power used to produce these lesions was at most a few watts, an order of magnitude less than that often used in clinical ablations. This finding probably is due to the fact that with the nearly full tissue immersion of the electrode provided by direct observational guidance, very little of the current is shunted to the low-impedance fluid media (in this case, saline), which is effectively a parallel resistance to the tissue.20,21

The data from this study on the effects of temperature were similar to that from adult animals,10 with one important exception. Haines and Watson10 found that in isolated myocardium, both the width and depth of their RF lesions increased linearly with temperatures above 50°C, whereas the in vivo data from immature myocardium from this study demonstrated a sigmoid effect of temperature on depth, with a saturation of the temperature effect above 80°C. Neither the experimental design of this study nor the literature provides data to differentiate the effects of myocardial developmental stage from the effects of using naturally perfused epicardium; however, there are data indicating an increased capillary density in immature myocardium,15 potentially providing excess coronary reserve and enhanced local heat transfer.

There are multiple structural and functional differences between adult and immature myocardium, some of which might have affected the response to the application of RF energy. Although the number of muscle fibers per capillary is larger in newborn human and many animal hearts than in adult hearts, because of a smaller myocyte diameter, the capillary density has generally been found to be higher in newborn than in adult hearts.15 Thus, myocardial blood content and flow have the potential to be somewhat higher in infant hearts. In addition, the intracellular space in infant myocardium has a lower density of many microstructures14 and presumably more water than adult myocardium. Since the impedance of both blood and saline are significantly lower than the impedance of tissue,20,21 the differences between immature and mature myocardium presumably change total tissue impedance characteristics and the response to RF energy. Differences in myocardial blood flow also might change heat transfer characteristics and affect both the rate and extent of RF heating, potentially accounting for the differences between the responses of width and depth to tip temperature and RF duration noted in this study.

**Increases in Lesion Size With Animal Growth**

Atrial and ventricular lesion sizes clearly increased simultaneously with cardiac and whole-body growth during the course of this study. Although the average dimensions of AV groove lesions did not change, the maximum lesion width was very large at the 1-month and late follow-ups. These findings are in distinct contrast to those found by previous investigators for RF lesions in adult dogs9,11-13 or for myocardial infarctions in many species22; however, this study provides only limited data to suggest a mechanism for the increase in
size. There are two possible mechanisms for an increase in lesion size: lesion stretch and actual growth of the lesion constituents. The differences between lesion size changes in the atria, AV groove, and ventricles may yield some insight into which mechanisms were operative. The fact that atrial lesion width increased by 1 month but only ventricular lesions were larger at late follow-up suggests that both mechanisms may have been operative. Almost all atrial lesions were transmural. They also were associated with large increases in lesion width, a trend toward a decrease in lesion depth, and replacement of normal atrial myocardium by fibrous and elastic tissue at 1 month, all changes consistent with scar formation accompanied by stretching and thinning of the affected area. In contrast, only some ventricular lesions were transmural. Although the transmural fibrous area was thinner than the surrounding myocardium, both the surrounding myocardium and the transmural area were thicker than in the atria, possibly accounting for less early stretch. Thus, the late increase in size of the ventricular lesions seems likely to be due to actual growth of both cellular and noncellular lesion constituents. Apparently, AV groove lesions, which did not change significantly in size, were not subject to significant stretching or growth or there was some offsetting lesion shrinkage that was less prominent than for lesions in other locations.

There are limited data on scar formation in immature hearts. Although there are no reports of notable myocardial scar enlargement after congenital heart surgery in humans, a single study specifically addressing the issue of myocardial scar maturation in developing dog hearts found that both atriotomy and ventriculotomy scars made in infant puppies more than doubled their length during an average of 5 months’ growth (human equivalent of 7 years), whereas scars in adult animals shrank by 20% to 30% during a similar follow-up period.22 Similar to this study, their results also demonstrated that atrial scars enlarged more than ventricular ones, but no data were presented to elucidate the mechanism of enlargement.23 Although the histological findings from this study cannot be used to assess quantitatively the question of cell division versus hypertrophy as a mechanism of lesion growth, the presence of fibrous and elastic tissue extensions into the normal myocardium of late lesions strongly suggests that growth was due at least in part to cell proliferation. Such a hypothesis is consistent with the observation that in contrast to adult hearts, both muscle and interstitial cells are actively dividing in infant animals and humans.14

Differences between the responses of atrial, AV groove, and ventricular tissue to the RF lesions may have been the result of differential completion of development or of differences in the amount of fibrous tissue normally present in these areas. For instance, the AV groove not only is composed of primarily fibrous tissue from early in development but has little postgestational cell division.14

**Clinical Implications**

**Accessory AV Pathways**

A number of factors, including technical problems with very small patients, the nearly 40% spontaneous loss of accessory pathway function by 1 year of age,24,25 and the fact that between 60% and 90% of infants will not have spontaneous recurrences of tachycardia after initial presentation,24,26 have led most investigators to recommend against RF ablation in infants before complete failure of medical therapy.3,27 Such recommendations also have been based on the observation that one reported late pediatric death after RF ablation of an accessory AV pathway was in a 5-week-old, 3.2-kg, former 32-week premature infant,28 who was noted to have significant damage to the ventricular myocardium despite attempted ablation on the atrial side of the AV groove. The findings from this study may help to explain these clinical observations by suggesting that any damage to ventricular myocardium may be associated with late lesion enlargement and relative histological invasiveness. Because of the small size of human infant hearts compared with the maximum lesion size of 5 to 8 mm produced by even the smallest catheters available,18,19 the recommendation to avoid intervention in the youngest patients probably should be followed until technical improvements allow for real-time assessment of lesion size during the ablation procedure. Until that time, the data from this and previous studies suggest that the potential for late growth may be restricted by avoiding ventricular muscle damage when ablating at the AV groove,1,3 keeping lesions as close as possible to the AV groove, and minimizing lesion size through smaller catheters,18,19 lower power applications (or if available lower temperature),10,17 and reduced RF application time.10 When procedures are necessary in infants because of failure of medical therapy, close echocardiographic and electrophysiological follow-up may be warranted.28

**Ventricular Muscle Ablation**

The data from this study and others,29,30 combined with the clinical data discussed above, suggest strongly that RF lesions in the ventricles of small infants should be avoided until medical therapies have been exhausted, or patient survival may be dependent on rapid arrhythmia control. Although surgical therapy has been acutely effective for some forms of medically resistant ventricular tachycardia,31 there are data to suggest that some surgical scars, in particular transmural ones,23 are as likely as RF lesions to cause late changes similar to those observed in this study.

**Atrial Muscle Ablation**

Atrial lesions did appear to increase in size during the first postablation month; however, further enlargement and histological invasion of fibrous tissue similar to that seen for the ventricular lesions were not noted at late follow-up. In addition, although the almost aneurysmal gross appearance of some atrial lesions did not cause any apparent hemodynamic, thrombotic, or significant electrophysiological abnormalities in this study, it may provide the substrate for later problems. Finally, previous reports of RF applications to atrial muscle in human infants during ablation of accessory pathways with an approach that emphasizes atrial side applications or when ablating an ectopic atrial tachycardia foci have not noted any late complications.3,6,27 Together these data suggest that ablation of atrial muscle in infants may not be as worrisome as ablation of ventricular muscle, but longer follow-up is necessary.
Study Limitations

Although there are numerous clinical implications to the observations made in this study, the results may not be directly applicable to RF ablation in human infants. First, the data do not indicate at what age the observed pathological changes in this study will no longer occur. In addition, the findings may be species specific and not generalizable to human infants. Finally, the advantages of RF ablation in some infants with medically refractory arrhythmias may outweigh the potential disadvantages highlighted in this study. Nevertheless, the data from this study and others should be taken into account when RF ablation is considered for the management of arrhythmias in infants.

Summary

The acute gross, histological, and thermodynamic characteristics of RF lesions made in infant hearts are similar to those described in adult hearts, with one exception: lesion depth may be slowed and limited by an enhanced vascular response to RF heating. However, at late follow-up, RF lesions made in immature myocardium reveal atrial and ventricular lesion enlargement and invasion of normal ventricular myocardium by fibrous and elastic tissue. These findings may have important implications for clinical RF ablation procedures in infants.

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