Nonreentrant focal activations in pulmonary veins in canine model of sustained atrial fibrillation

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Recent studies show that paroxysmal atrial fibrillation (AF) in humans may be initiated by trains of rapid discharges from the pulmonary veins (PVs) (11) or the ligament of Marshall (LOM), which is located in the posterior wall of the left atrium (LA) (14). Our recent canine experimental study (40) demonstrated repetitive rapid activations within the LOM and the PVs in pacing-induced sustained AF, suggesting that the LOM and PVs play a role in the maintenance of this arrhythmia. However, because only a few electrodes were used to record from the PVs in that study, it was unclear if these rapid activations were due to focal discharge or microreentry. Spach et al. (33) studied human atrial tissues from patients whose ages ranged 1–70 yr. In these tissues, anisotropic propagation was necessary for a reentrant circuit to be contained within an area of 50 mm². In conditions leading to obliteration of side-to-side electrical coupling between fibers (e.g., aging and chronic hypertrophy), microreentry may occur within an even smaller area (0.6 mm in width; 2.6 mm in length). These data indicate that if we were to demonstrate microreentrant circuit, a high-density electrode mapping array is necessary. Therefore, we developed a new computerized mapping system with a high-density electrode mapping array to map the detailed patterns of activation in the PVs and atria of dogs with sustained AF. The interelectrode distance was 1 mm in five dogs and 2.5 mm in one dog. Our purpose was to map PV activity during AF and relate it to possible arrhythmia mechanisms.

METHODS

This research protocol was approved by the Institutional Animal Care and Use Committees and conforms to the American Heart Association Guidelines. Mongrel dogs (18–25 kg) were used in the study.

Chronic pacing to induce sustained AF. Sustained AF, defined as AF that persists for 48 h off pacing, was induced by intermittent rapid pacing (40) from the LA (N = 6). During the first surgery, we performed a thoracotomy via the left fourth intercostal space. A screw-in bipolar pacing lead was inserted into the LA appendage and connected to a Medtronic Itrel II model 7424 or Itrel III model 7425 neurostimulator implanted in a subcutaneous pocket. After ~1 wk, the pulse generator was programmed to burst pace at a pacing interval

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of 50 ms for 5 s with an output of 3.0 V, followed by a 2-s period without pacing. To simulate clinical practice in managing patients with sustained AF, we used digoxin (0.005–0.007 mg·kg\(^{-1} \cdot \text{day}^{-1}\)) to control ventricular rate in dogs 1–5. In dog 6, digoxin was not given. The pacemaker was turned off periodically, at least once a week, to evaluate rhythm. If AF was induced, we kept the pacemaker off to determine if AF was sustained for >48 h. When sustained AF was documented off pacing, the Itrel pacemaker was turned back on, and the dogs were scheduled for computerized mapping studies.

**Computerized mapping.** Under pentobarbital general anesthesia, the dogs were endotracheally intubated and ventilated. The chest was opened via a left thoracotomy. The heart was suspended in a pericardial cradle. Part of the pericardium was removed to expose the PV-LA junction and the PVs.

For studying the first dog with sustained AF induced by LA pacing, we used a 158-channel bipolar mapping plaque with a 2.5-mm interelectrode distance to separately map the PVs, LA posterior wall, LA anterior wall, and RA anterior wall. The electrodes were connected to a 480-channel mapping system. The same system was used in a previous report (40). For studying the remaining five dogs with sustained AF induced by LA pacing and five normal dogs, we used a newly developed 1,792-channel computerized mapping system (Unimap; Uniservices). Four electrode patches, each with 448 electrodes with 1-mm interelectrode distance covering a 2.5-cm area (Fig. 1A). A new 480-channel mapping system was used in the study. The same system was used in a previous report (40). For studying the remaining five dogs with sustained AF induced by LA pacing and five normal dogs, we used a newly developed 1,792-channel computerized mapping system (Unimap; Uniservices). Four electrode patches, each with 448 electrodes with 1-mm interelectrode distance covering a 2.5-cm area (Fig. 1A). A 158-channel bipolar mapping plaque was used in the study.

**Table 1.** The cycle length and dominant frequency during chronic pacing-induced sustained atrial fibrillation

<table>
<thead>
<tr>
<th>Dog</th>
<th>PVs with focal activities</th>
<th>LSPV</th>
<th>LIPV</th>
<th>RIPV</th>
<th>LAPW</th>
<th>LAAW</th>
<th>RAAW</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LSPV</td>
<td>78 ± 3</td>
<td>82 ± 5</td>
<td>79 ± 5</td>
<td>80 ± 6</td>
<td>87 ± 5</td>
<td>111 ± 7</td>
</tr>
<tr>
<td>2</td>
<td>LSPV, LIPV, RIPV</td>
<td>79 ± 5</td>
<td>79 ± 4</td>
<td>91 ± 6</td>
<td>90 ± 7</td>
<td>97 ± 6</td>
<td>104 ± 9</td>
</tr>
<tr>
<td>3</td>
<td>LSPV, RIPV</td>
<td>85 ± 4</td>
<td>92 ± 3</td>
<td>80 ± 2</td>
<td>89 ± 8</td>
<td>94 ± 6</td>
<td>102 ± 5</td>
</tr>
<tr>
<td>4</td>
<td>LSPV, LIPV, RIPV</td>
<td>79 ± 4</td>
<td>81 ± 6</td>
<td>83 ± 4</td>
<td>82 ± 6</td>
<td>90 ± 4</td>
<td>104 ± 7</td>
</tr>
<tr>
<td>5</td>
<td>LSPV, RIPV</td>
<td>78 ± 3</td>
<td>88 ± 3</td>
<td>81 ± 6</td>
<td>86 ± 3</td>
<td>89 ± 4</td>
<td>107 ± 4</td>
</tr>
<tr>
<td>6</td>
<td>LIPV</td>
<td>94 ± 5</td>
<td>77 ± 2</td>
<td>85 ± 6</td>
<td>92 ± 5</td>
<td>94 ± 7</td>
<td>116 ± 5</td>
</tr>
<tr>
<td>Means ± SD</td>
<td></td>
<td>82 ± 6†</td>
<td>83 ± 6†</td>
<td>83 ± 4†</td>
<td>87 ± 5†</td>
<td>92 ± 4†</td>
<td>107 ± 5</td>
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**Dominant frequency, Hz**

<table>
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<tr>
<th></th>
<th>13.3 ± 1.0</th>
<th>12.0 ± 0.8</th>
<th>12.8 ± 0.5</th>
<th>12.3 ± 0.8</th>
<th>11.6 ± 1.3</th>
<th>9.0 ± 1.1</th>
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<tr>
<td>2</td>
<td>12.6 ± 0.8</td>
<td>12.5 ± 1.1</td>
<td>11.4 ± 1.0</td>
<td>11.0 ± 1.0</td>
<td>10.5 ± 0.9</td>
<td>9.7 ± 0.5</td>
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<td>3</td>
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<td>10.9 ± 0.6</td>
<td>12.4 ± 0.4</td>
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<td>9.8 ± 0.7</td>
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<td>12.5 ± 0.6</td>
<td>13.0 ± 0.5</td>
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<td>12.2 ± 0.9</td>
<td>11.2 ± 0.5</td>
<td>9.9 ± 1.0</td>
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<tr>
<td>5</td>
<td>13.0 ± 0.5</td>
<td>11.8 ± 0.9</td>
<td>12.5 ± 0.8</td>
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<tr>
<td>Means ± SD</td>
<td>12.6 ± 0.5†</td>
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<td>12.1 ± 0.5†</td>
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PV, pulmonary vein; LSPV, left superior PV; LIPV, left inferior PV; RIPV, right inferior PV; LA, left atrium; LAPW, LA posterior wall; LAAW, LA anterior wall; RAAW, right atrium anterior wall. *P < 0.05 compared with LAAW; †P < 0.01 compared with RAAW.
the horizontal neighbors before digitization, the same electrode patch can record 420 bipolar electrograms. Using these four electrode patches, we simultaneously mapped one of the PVs, the RA anterior wall, the LA anterior wall, and the LA posterior wall, which includes the LOM (Fig. 1, A and B). Serial transverse sections of the PVs were stained using Masson trichrome, anti-tyrosine hydroxylase (anti-TH) (3), and anti-connexin40 antibodies (37). The signals were filtered with a 0.05-Hz high-pass filter and were digitized at 1,000 samples/s with 12 bits of accuracy. At the end of each study, the PVs were fixed according to previously published protocols (3). Serial transverse sections of the PVs were stained using Masson’s trichrome, anti-tyrosine hydroxylase (anti-TH) (3), and anti-connexin40 antibodies (37).

Data analyses. For each dog, we analyzed nine runs of AF (3 runs for each of the 3 PVs, 8 s/run). We selected the absolute maximum rate of velocity change over time (dV/dt) as the time of local activation for bipolar electrograms (2, 17). For unipolar electrograms, the most negative dV/dt was used. Dynamic display (17) and isochronal maps were used to analyze the activation sequence. A focal activation is defined as an activation pattern with wavefronts spreading outward in all directions from a recording site. An activation wavefront that originates from the edge of the mapped region is not considered focal. The AF cycle length was calculated as the mean of all AF cycle lengths within one area. We also performed fast Fourier transforms on unipolar and bipolar electrograms from different regions to determine the dominant frequency (the highest power of frequency spectrum) of the electrograms (19, 40).

Data are presented as means ± SD. ANOVA and the Newman-Keuls test were used for multiple comparisons. A P ≤ 0.05 is considered significant.

**RESULTS**

**Induction of sustained AF.** AF was induced in 23 ± 7 days by LA pacing. These dogs were studied 7 ± 2 days after sustained AF was documented. Immediately before the Itrel was turned on (~1 wk after the first surgery), the average sinus rate was 134 ± 12 beats/min in the first five dogs and 150 beats/min in dog 6. After sustained AF was induced, the ventricular response rate was 219 ± 48 beats/min for the first five dogs and 240 beats/min for dog 6 while the dogs were ambulatory. During the second surgery, the ventricular rate in the AF group was 163 ± 31 beats/min for the first five dogs and 146 beats/min for dog 6. There was no significant difference in heart weight between the AF group (260 ± 12 g) and the control group (189 ± 19 g). All dogs were in AF throughout the mapping studies.

**Sustained AF induced by LA pacing.** We mapped three PVs in each of the six dogs with sustained AF. Among them, 12 PVs (5 LSPVs, 3 LIPVs, 4 RIPVs) demonstrated rapid repetitive focal activities. The remaining six PVs showed activations originating from the LA and propagating into the PVs. In each dog, at least one PV showed focal activity. Table 1 summarizes the activation cycle lengths in the PVs mapped.

Among the 12 PVs with rapid focal activity, 10 showed a single focal site, and the other two PVs...
demonstrated two independent foci. Activation initiated from the focal site spread centrifugally to the distal part of the PV and the PV-LA junction (Fig. 2). This kind of focal activation pattern was seen in 7 of 12 PVs. The horizontal propagation velocity was 1.1 ± 0.49 m/s. In comparison, the vertical propagation velocity was 0.74 ± 0.32 m/s ($P < 0.05$). The propagation from the focal source to the periphery was associated with intermittent conduction delay and blocks. In the same recording, some activations propagated from the LA-PV junction to the PV (Fig. 2B), indicating that the focal source in the PV and the wavefronts in the LA were competing to activate the PV.

A second kind of activation pattern is shown in Fig. 3. In this pattern, the central portion of the PV appeared to activate simultaneously over a wide area. The activation then spread primarily vertically to the distal PV and LA. This kind of focal activation pattern was seen in 5 of 12 PVs. Similar to that shown in Fig. 2, the propagation away from this central portion was associated with intermittent conduction blocks. Within the same recording, the earliest activation usually appeared at the same general location within the PV during the 8-s recording period (Fig. 3). There were usually one or two unipolar electrograms in the early site with QS morphology (channels d1 and d2 in Fig. 3D), compatible with the electrograms found at the origin (the earliest site) of electrical activity (13). This QS pattern, however, could also be compatible with propagation across myocardial fibers (34). The QS morphology later changed to rS morphology after the third activation. On the sixth activation, the electrogram at site e occurred roughly at the same time as that at site d2, and earlier than that at site d1. The QS pattern was not found in electrograms from other regions. Repetitive focal activations often had irregular cycle lengths.
In no PVs did we identify reentrant wavefronts. The sites of the earliest activation in the LSPV, LIPV, and RIPV were located 8 ± 6, 6 ± 3, and 6 ± 3 mm, respectively, distal to the PV-LA junction. Conduction delay and block within PVs and between PVs and LA were often observed (Figs. 2B and 3D).

In all recordings, two or more wavelets, including both wandering wavelets and organized reentry, were observed in the LA. In contrast, a single broad wavefront often propagated across the RA. These findings reproduced those reported previously from our laboratory (40). Figure 4A shows an example of an isochronal map of four simultaneously mapped regions (1,792 unipolar electrodes used) during sustained AF. The LIPV showed a focal source of activation (black arrow in Fig. 4A). Approximately 13–17 ms after the onset of LIPV activation, two wavefronts were seen in the LA posterior wall. This was followed by the activation of the LA anterior wall 20–30 ms later, also with two wavefronts. The RA anterior wall was then activated by a large and coherent wavefront that propagated from the RA free wall to the RA appendage (Fig. 4A). The LA wavefronts were complicated and did not follow a fixed direction of propagation. Therefore, while PV appeared to activate faster than LA, the mapping data did not prove that the reentrant activities in LA represent passive activation from PV.

Figure 4B shows the corresponding dominant frequency map. Areas of high and low dominant frequencies (black and red arrows, respectively) were found in the PV, compatible with rapid activation at the focal site and conduction block to the distal PV as shown in Fig. 3D. The dominant frequencies were lower in the LA and RA than in the PV.

Table 1 shows the activation rates and dominant frequencies of all dogs studied. Mean activation cycle lengths in the PVs and LA posterior wall were significantly shorter than those in the LA anterior wall and RA anterior wall. There were no significant differences in mean cycle length among the three PVs and LA posterior wall where the LOM was located. Fast Fourier transforms analyses showed a gradient of dominant frequency distribution with the highest frequency in the PVs and LA posterior wall followed by the LA anterior wall and then the RA anterior wall.

Activation patterns of AF in normal dogs. A total of 15 PVs were mapped in 41 episodes of AF and 18 runs of sinus rhythm in five normal dogs. Each episode of AF spontaneously terminated during the study. In all recordings of acute AF and sinus rhythm, the earliest activation repetitively initiated in the LA posterior wall and then propagated to the PVs in a single large wavefront, resulting in the proximal-to-distal venous activation pattern (Fig. 5, A and D). Focal activation or reentrant wavefronts were not observed in the PVs during the short-lived AF episodes. The LA usually had one or two wavefronts (Fig. 5, B and E). In the RA anterior wall, the activation pattern was similar to that of pacing-induced sustained AF, with a single wavefront propagating across the mapped region. There were no conduction blocks between the PV and LA during AF (Fig. 5C) or sinus rhythm (Fig. 5F).

Histological examination. Histological examination of the PVs shows that cardiac muscle cells were found in all proximal PVs of both AF and normal dogs. Figure 6, A and B, shows cross sections of a LSPV 12 and 6 mm from the PV-LA junction, respectively. Isolated muscle bundles (arrow) are seen in Fig. 6A. In Fig. 6B,
the entire PV is surrounded by atrial myocytes (arrow) with complex fiber orientation. Figure 6C is from the same LSPV 8 mm beyond the PV-LA junction. Abrupt changes of fiber orientations are seen (between white and black arrows). Isolated muscle bundles are observed in distal PVs (Figs. 6, A and D). The muscle fibers are usually detectable \(\leq 15\) mm above the LA-PV junction. Figure 6, C and D, also shows increased fibrous tissues between the muscle bundles. These fibrous tissues may have reduced cell-to-cell coupling. However, connexin40 staining showed that connexin is present in the mapped PVs (Fig. 6E). There were sympathetic (TH-positive) nerves within the muscular layer of the PVs (Fig. 6F).

**DISCUSSION**

In this study, we demonstrated that rapid focal activations are present in the PVs during sustained AF induced by LA pacing. In contrast, focal activations are not found in the PVs during nonsustained AF induced acutely in normal dogs. There was an activation rate gradient during sustained AF. The PVs and LA posterior wall (including the LOM) activated at shorter cycle lengths than the LA anterior wall and RA anterior wall. These findings support the hypothesis that the PVs and LOM are sources of rapid focal activation in a canine model of pacing-induced sustained AF (40).
Mechanisms of the focal activations. Both PVs (25, 26, 29, 32) and the LOM (16, 31) have muscle sleeves that connect to the LA. In the present study, we mapped the PVs with 1-mm resolution and showed focal discharges within the PVs, compatible with active participation of venous muscle sleeves in the maintenance of sustained AF. An important negative finding is that we failed to demonstrate any evidence of microreentry within the mapped epicardial surface. According to Spach et al. (33), an area of 50 mm² is usually needed to support a microreentrant circuit in human atria. Even in conditions leading to obliteration of side-to-side electrical coupling, microreentry still needs 1.6 mm² (0.6 mm width; 2.6 mm length) of tissue to maintain. A 1-mm resolution should be sufficient for detecting any epicardial reentrant circuits. Furthermore, our histological studies showed that the thickness of the muscle sleeves within the PV was <1 mm. Therefore, transmural reentry with focal epicardial breakthrough is also an unlikely mechanism to account for the focal activation patterns within the PVs.

Embryological development of the PVs is closely related to the development of the sinus venous segment of the heart (1, 38). Masani et al. (21) showed that node-like cells are present in the myocardial layer of the PV of rats. Ito et al. (15) demonstrated spontaneous diastolic depolarization in rabbit sinocaval cells. Cheung (7) reported that isolated PVs were capable of independent pacemaking activity. Chen et al. (5) demonstrated rapid arrhythmogenic activity in canine PVs. β-Adrenergic blockers, calcium channel blockers, adenosine, and acetylcholine suppressed these spontaneous activities. A recent whole cell clamp study (6) showed that isolated PV cells from dogs with rapid atrial pacing demonstrated faster automaticity and higher rates of afterdepolarizations than those from control dogs. These data indicate that rapid atrial pacing might result in proarrhythmic remodeling of PV cells, including automaticity and afterdepolarizations.

While our dogs did not have clinical evidence of heart failure, the ventricular response rates during AF were over 200 beats/min. Therefore, a component of ventricular tachycardioinmyopathy cannot be totally excluded. Li et al. (18) demonstrated significant remodeling of ion channels in dogs with tachycardia-induced heart failure. These ionic changes, which include decreased atrial transient outward K⁺ current, L-type Ca²⁺ current, and slow delayed rectifier K⁺ current and increased Na⁺/Ca²⁺ exchanger current, might promote triggered activity.

We propose that automatic foci and triggered activities could account for the focal activation patterns..

Fig. 6. PV histology. A–D: results of trichrome staining. A and B: distal and proximal, respectively, of LSPV in dog 2. White arrows show cardiac muscle with fibers oriented perpendicular to blood flow, accounting for the rapid horizontal spread of excitation in Fig. 2. C: muscle bundles next to each other have different orientations (black and white arrows). D: insulated muscle bundles (black arrows) surrounded by collagen (blue color). E: connexin40 (brown color) staining of the LSPV in a dog with sustained AF. F: sympathetic nerve fibers (arrow) stained with tyrosine hydroxylase antibody. Magnification of objective: ×10 for A, B, and D, ×20 for C and E, and ×40 for F. The horizontal bar at the lower left corner of each panel is 100 µm long.
observed in the present study. Whether or not the sympathetic nerves in the PVs played a role in maintaining automatic activity or triggered activities is unclear.

Focal source hypothesis of AF. It is known that aconitine administration to the atria can induce rapid focal discharge and AF (28, 30). When this focal source is isolated by the application of a clamp, the remainder of the atria immediately resumes sinus rhythm, while tachycardia persists at the aconitine site (23). These studies indicate that rapid focal activation can lead to AF and eliminating this focal source may result in AF termination. Mandapati et al. (19) induced AF in isolated sheep hearts in the presence of acetylcholine. They demonstrated that the highest dominant frequency was most often localized to the posterior LA, near or at the PV ostium. In addition, there was a gradient of dominant frequency between the LA and the RA, suggesting that a high frequency source might be responsible for AF in that model (20). In human patients, the PVs (4, 11), the LOM (14), and the superior vena cava (36) are sources of rapid activations in paroxysmal AF. Radiofrequency catheter ablation of the PVs or LOM can result in the cure of this arrhythmia.

While rapid activations in the PV might contribute to the initiation or maintenance of paroxysmal AF or AF induced by acetylcholine, the mechanisms of sustained (chronic) AF remained unclear. In dogs with pacing-induced sustained AF, Morillo et al. (24) reported that an area in the posterior LA was uniformly shown to have the shortest AF activation cycle length. That area was near the PV-LA junction. However, the activation cycle lengths within the PVs were not determined. Kligfield et al. (10) subsequently extended their observations by directly recording from the PV, the LOM, and the atria. The results showed that the PV and the LOM activated at shorter activation cycle lengths than the LA, which in turn had a shorter activation cycle length than the RA during sustained AF. These findings were also compatible with many previous animal and clinical studies. For example, Spach et al. (32) showed that it is possible for the LA to be in fibrillation while the RA is in tachycardia at the same time. Fieguth et al. (10) reported that a local compartment operation with suture lines around the hilum/PVs of the LA resulted in a surgical cure for AF in a sheep model. In humans, Harada et al. (12) demonstrated repetitive rapid activations in the orifice of the left PVs in AF due to mitral valve diseases. Isolation of the PVs may prevent the recurrence of AF (22, 27, 35, 39). These data suggest that thoracic veins, including PVs and LOM, may play important roles in the maintenance of sustained AF.

Digoxin and possible mechanisms of focal PV activation. In addition to rapid pacing, AF dogs 1–5 also received digoxin to control ventricular rates. We chose digoxin because it is commonly used in human patients to achieve rate control during AF. Therefore, using digoxin in dogs with AF simulates the clinical practice and increases the relevance of this study to the human disease. Use of digoxin, however, may not be the best clinical strategy, because previous studies have shown that ouabain infusion can trigger the onset of rapid repetitive activity from the distal PV (8). It is possible that in human patients and this canine model, the use of digoxin might have promoted the focal discharge from the PVs.

While digoxin might have facilitated the development of focal activities within the PVs, it is unlikely that the focal activations detected in this study were entirely secondary to the use of digoxin. In one AF dog, digoxin was not used. However, focal PV activity was also observed. Chen et al. (6) showed that rapid atrial pacing could result in proarrhythmic remodeling of the PV cells, resulting in increased automaticity and afterdepolarizations. These changes were demonstrated in the absence of digoxin. Furthermore, Duytschaever et al. (9) recently reported that digoxin had no effect on the rate or stability of pacing-induced AF in a goat model. In contrast, infusion of verapamil had a direct proarrhythmic effect, including shortening the AF cycle length and reducing the refractory period of the atria. These data support the use of digoxin, not verapamil, for rate control in dogs with pacing-induced AF.

Limitations. A limitation of this study was that we did not perform PV and LOM ablations to determine if elimination of the focal activation in these structures would terminate AF. The present study was conducted in a canine model with sustained AF induced by LA pacing. Generalization of these results to human sustained AF or other canine models of AF should be made with caution. While we demonstrated nonreentrant focal activities in the mapped region, this study could not rule out the possible presence of reentry at a time when mapping was not performed. It also does not rule out reentrant activities in areas not mapped, such as the right superior PV or the posterior wall of the other PVs.

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REFERENCES


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